

Remarks/Arguments

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 119-121 and 123 are pending in this application and are rejected on various grounds. Claim 119 has been amended to correct a formality. The rejections to the presently pending claims are respectfully traversed.

Priority

Based on the discussions below, Applicants maintain that they rely on the gene amplification assay for patentable utility of the instant invention, which was first disclosed in U.S. Provisional Application 60/141037, filed June 23, 1999, priority to which has been claimed in this application. Hence, the present application is entitled to at least the priority date of **June 23, 1999**.

Claim Objection

Claim 119 was objected to since the parentheses around "SEQ ID NO: 326" were to be removed.

Accordingly, Applicants have removed the parentheses and request the withdrawal of this objection.

Claim Rejections – 35 USC § 101 and 35 USC § 112, first paragraph

Claims 119-121 and 123 remain rejected under 35 U.S.C. §101 allegedly because "the instant application does not disclose a specific and substantial biological role of this protein or its significance."

Claims 119-121 and 123 remain further rejected under 35 U.S.C. §112, first paragraph allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention". Applicants respectfully disagree with and traverse these rejections.

The Examiner asserts that the invention lacks "specific" and "substantial" utility. The Examiner adds on page 4 of the Final Office action dated July 28, 2004 that "an increase in nucleic acid copy number is not predictive of a similar association for protein is supported by the

prior art" and cites references Pennica *et al.*, Konopka *et al.* and Haynes *et al.* for support. Regarding the Hanna and Mornin reference, the Examiner says on page 5, line 5 that their data is not persuasive because "it (is) difficult to extrapolate data from one protein, or its encoding gene, to another". Applicants respectfully traverse these rejections, for the reasons outlined below.

Utility Standard

In interpreting the utility requirement, in *Brenner v. Manson*¹ the Supreme Court held that the quid pro quo contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or her invention, i.e. a utility "where specific benefit exists in currently available form."² The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."³

Later, in *Nelson v. Bowler*⁴ the CCPA acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."⁵

In *Cross v. Iizuka*⁶ the CAFC reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less

¹ *Brenner v. Manson*, 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

² *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

³ *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

⁴ *Nelson v. Bowler*, 626 F. 2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

⁵ *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

⁶ *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, i.e. there is a reasonable correlation there between.⁷ The court perceived "No insurmountable difficulty" in finding that, under appropriate circumstances, "*in vitro* testing, may establish a practical utility."⁸

The case law has also clearly established that applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.⁹ The PTO has the initial burden that applicants' claims of usefulness are not believable on their face.¹⁰ In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."^{11, 12}

Compliance with 35 U.S.C. §101 is a question of fact.¹³ The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration.¹⁴ Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility.

Absolute predictability is not a requirement. Only after the Examiner made a proper *prima*

⁷ *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

⁸ *Id.*

¹⁰ *Ibid.*

¹¹ *In re Langer*, 503 F.2d 1380, 1391, 183 U.S.P.Q. (BNA) 288, 297 (CCPA 1974).

¹² See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

¹³ *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984).

¹⁴ *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

facie showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

The well established case law is clearly reflected in the Utility Examination Guidelines (“Utility Guidelines”)¹⁵, which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted “specific, substantial, and credible utility” or a “well-established utility.” Under the Utility Guidelines, a utility is “specific” when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the “substantial utility” standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase “immediate benefit to the public” or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be “currently available” to the public in order to satisfy the utility requirement. “Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a “‘substantial’ utility.”¹⁶ Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,¹⁷ gives the following instruction to patent examiners: “If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.”

Proper Application of the Legal Standard

Applicants maintain that the specification provides sufficient disclosure to establish a specific, substantial and credible utility for the instantly claimed antibodies to the PRO1281 polypeptide of SEQ ID NO: 326.

¹⁵ 66 Fed. Reg. 1092 (2001).

¹⁶ M.P.E.P. §2107.01.

¹⁷ M.P.E.P. §2107 II(B)(1).

As a preliminary matter, Applicants respectfully submit that it is not a legal requirement to establish a "necessary" correlation between an increase in the copy number of the mRNA and protein expression levels that would correlate to the disease state or that it is "imperative" to find evidence that protein levels can be accurately predicted. As discussed above, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, the question is not, whether a necessary or even "strong" correlation between an increase in copy number and protein expression levels exists, but whether it is more likely than not that a person of ordinary skill in the pertinent art would recognize such a positive correlation. Applicants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

On page 5, third paragraph of the Final Office action dated July 28, 2004, the Examiner asserts that,

"(t)he fact that a particular gene is not amplified, in the absence of further supporting evidence from Applicants, does not provide a specific and substantial utility, or a well-established utility for that DNA. All it demonstrates is that that particular DNA is not involved in that particular cancer....Applicants have not demonstrated how the genomic DNA for PRO1281 fits into this equation...Any genomic DNA can be used for this purpose since all DNA levels will either increase, decrease, or remain the same," emphasis added.

Applicants strongly disagree. Applicants clearly presented supportive evidence and showed that the gene encoding for PRO1281 was significantly amplified, $2^{1.07}$ - $2^{1.15}$ fold, or 2.099 fold to 2.219-fold, in two out of two colon tumors studied (see Example 170 (page 554, Table 9C)). These values are considered significant based on the Declaration by Dr. Audrey Goddard (submitted herewith). Therefore the DNA encoding PRO1281 is clearly involved in colon cancer. The instant application is directed to antibodies to native PRO1281 polypeptides. As discussed below, Applicants show that the art clearly shows that it is "more likely than not" for the corresponding polypeptide of an amplified DNA to also be overexpressed in the same tumor. Therefore, Applicants submit that antibodies to PRO1281 also have utility as a diagnostic markers in human colon cancers.

The Examiner asserts that the art supports that "an increase in nucleic acid copy number is not predictive of a similar association for protein" based on the teachings of prior art references Pennica *et al.*, Konopka *et al.* and Haynes *et al.* Applicants respectfully traverse.

Applicants draw attention to Pennica's showing that "a correlation between DNA amplification and over-expression exists for the *WISP*-1 gene" in 84% of the tumors examined. While Pennica discloses a lack of correlation for the *WISP*-2 gene, Pennica teaches nothing regarding such a lack of correlation in genes in general. That is, Pennica's teachings are specific for the *WISP* family of genes, and are not directed to genes in general. Similarly Konopka only addresses the *abl* gene, again not genes in general. Applicants submit that submit that the Examiner has generalized a very specific result disclosed by Konopka *et al.* to cover all genes. Konopka *et al.* actually state that "[p]rotein expression is not related to amplification of the *abl* gene but to variation in the level of *bcr-abl* mRNA produced from a single Ph¹ template." (See Konopka *et al.*, Abstract, emphasis added). Therefore, Konopka is not an appropriate reference for making a *prima facie* case for lack of utility. The Utility Guidelines requires that for a *prima facie* showing of lack of utility, the Examiner has to provides evidence that it is **more likely than not** that a lack of correlation between protein expression and gene amplification exists, in general. Accordingly, Applicants respectfully submit that Pennica and Konopka teach nothing of the correlation between gene amplification and polypeptide over-expression in general.

The Examiner adds that "Haynes *et al.* studied 80 proteins... and found no strong correlation between proteins and transcript levels." Applicants respectfully traverse and point out that, on the contrary, Haynes teaches that "**there was a general trend** but no strong correlation between protein [expression] and transcript levels" (see Figure 1) (Emphasis added). Haynes studied 80 *yeast* proteins to show that "protein levels cannot be **accurately** predicted from the level of the corresponding mRNA transcript" (Emphasis added) (see page 1863, paragraph 2.1, last line). For example, in Figure 1, Haynes shows that there is a positive correlation between mRNA and protein amongst **most** of the 80 yeast proteins studied but the Figure shows that the correlation is "not linear" and hence, "one cannot **accurately** predict protein levels from mRNA levels." But, it is not a legal requirement to accurately predict protein levels from the evidence presented nor to establish a "necessary" correlation between an increase in the copy number of the mRNA and protein expression levels, as discussed above. Moreover, in Figure 1 or Haynes,

very few data points deviated or scattered away from the expected normal or showed a lack of correlation between mRNA: protein levels. Therefore, the Haynes data, in fact, meets the "more likely than not standard" and shows that a positive (although not strong) correlation exists between mRNA and protein. This is all that's needed to meet the "more likely than not" evidentiary standard. When the proper legal standard is used, this clearly supports Applicants' position. Again, accurate prediction is not the standard. Thus, Applicants submit that the Examiner's rejection is based on a misunderstanding of the scientific data presented in Haynes *et al.*

Therefore, contrary to the Examiner's assertion, the cited art does not support the teaching that "nucleic acid copy number is not predictive of a similar association for protein" in general. In fact, Pennica's, Konopka's and Haynes' teachings do not provide sufficient reasons to doubt the Applicants statements regarding the utility of PRO1281 antibodies as a marker to diagnose colon cancer.

In fact, the correct test for utility is whether it is "more likely than not" that, a positive correlation exists between proteins and nucleic acid levels. Based on the teachings of Orntoft, Pollack and Hyman (previously submitted) and the Haynes reference cited by the Examiner, a vast number of genes studied in these references indicated that "there was a general trend between increased protein expression and transcript levels," which meets the "more likely than not" standard and clearly shows that increased gene levels correlate well, in most genes, with increased expression of the protein.

Applicants further submit that, even if there were no correlation between gene amplification and increased mRNA/ protein expression, (which Applicants expressly do not concede), a polypeptide encoded by an amplified gene in cancer would still have a specific, substantial, and credible utility as explained below. As the Declaration of Dr. Avi Ashkenazi (submitted with Applicants' Response filed June 4, 2004) explains:

"even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment."

Additional supporting evidence for such a utility is presented in a real-world example in an article by Hanna and Mornin (submitted with Applicants' Response filed June 4, 2004), which

demonstrates a use for the breast cancer marker HER-2/neu. Hanna and Mornin teach that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH), as well as, the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it. Thus, as evidenced by the Ashkenazi Declaration and the teachings of Hanna and Mornin, one skilled in the art would appreciate that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, were not over-expressed. This leads to better determination of a suitable therapy for the tumor. Such testing is for the purpose of characterizing not the PRO1281 polypeptide, but the tumors in which the gene encoding PRO1281 is amplified. Therefore, the PRO1281 polypeptide is also useful in tumor categorization, the results of which become an important tool in the hands of a physician enabling the selection of a treatment modality that holds the most promise for the successful treatment of a patient.

Based on the gene amplification data presented for PRO1281 in Example 170 of the specification, and all the submitted evidence, there is ample support for the Applicants' position that increased gene amplification levels, more likely than not, predict increased mRNA and polypeptide levels. One of skill in the art would therefore reasonably expect, based on: (a) the gene amplification data for the PRO1281 gene, (b) the supportive evidence in the Declarations submitted, and, (c) the supportive articles presented by the Applicants which were available in the art at the time of filing of the instant application, that the PRO1281 polypeptide is most likely, concomitantly, overexpressed in certain colon tumors, just like the PRO1281 gene, and is therefore antibodies to PRO1281 are useful as tumor markers for certain colon cancers. Even in the event that the PRO1281 polypeptide were found not to be overexpressed in the colon tumors where the PRO1281 gene were amplified, (a position expressly not conceded to), the PRO1281 polypeptide, and therefore its antibody, is still useful as a marker in tumor categorization and becomes an useful tool, enabling the physician to decipher appropriate lines of treatment for the cancer patient, which is a real-life utility.

This opinion expressed by Dr. Ashkenazi in his Declaration, who is an expert in the field of Cancer biology and is a Director of Molecular Oncology at Genentech, Inc. is based on his

factual findings and is supported by Hanna and Mornin's HER-2 gene/ neu protein study. Moreover, the case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew.¹⁸ "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument"¹⁹ Furthermore, the Federal Court of Appeals held in *In re Alton*, "[w]e are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner."²⁰ Applicants also respectfully draw the Examiner's attention to the Utility Examination Guidelines²¹ which states that,

"Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered".

Therefore, barring evidence to the contrary regarding the above statement in the Ashkenazi declaration, this rejection is improper under both the case law and the Utility guidelines.

Thus, Applicants submit that they have demonstrated utility for the PRO1281 polypeptide and its antibodies as a colon tumor marker based on gene amplification evidentiary data in the specification, and also based on supportive literature which was available to one of skill in the art at the time of filing. Moreover, the Patent Office has failed to meet its initial burden of proof that the Applicant's claims of utility are not "substantial" or "specific" based on the prior art papers presented by the Examiner, since they do not address general trends or genes "in general" and instead address isolated cases.

¹⁸ *In re Rinehart*, 531 F.2d 1084, 189 USPQ 143 (CCPA 1976) and *In re Piasecki* 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985).

¹⁹ *In re Alton* 37 USPQ2d 1578 (Fed. Cir. 1966) at 1584 quoting *In re Oetiker* 977 F.2d at 1445, 22 USPQ2d at 1444.

²⁰ *In re Alton*, supra.

²¹ Part II B, 66 Fed. Reg. 1098 (2001).

Applicants further submit that based on the claimed utility for PRO1281 polypeptides and its antibodies in the diagnosis of colon cancer, and the collective teachings in the specification, one of skill in the art would know exactly how to make and use the claimed antibodies for the diagnosis of colon cancer. Accordingly, the present 35 U.S.C. §101 and §112, first paragraph utility and enablement rejections should be withdrawn.

Claim Rejections – 35 USC § 102

A. Claims 119-121 and 123 are rejected under 35 U.S.C. §102(b) as being anticipated by Baker (WO99/63088- dated December 1999).

Based on the discussions above, Applicants maintain that they are entitled to at least the effective priority date of **June 23, 1999**, and therefore, Baker is neither 35 U.S.C. §102(b) nor 102(a) art. Hence, Applicants respectfully request that this request be withdrawn.

B. Claims 119-121 and 123 are rejected under 35 U.S.C. §102(a) as being anticipated by Tang (WO 01/53312- dated July 2001).

Based on the discussions above, Applicants maintain that they are entitled to at least the effective priority date of at least **June 23, 1999**, and thus, Tang is not prior art. Thus, this rejection should be withdrawn.

Claim Rejections – 35 USC § 103

A. Claims 119-121 and 123 are rejected under 35 U.S.C. §103(a) as being unpatentable over Weimann (2001) in view of Baker (1999).

For the reasons discussed above under utility, Applicants believe that they are entitled to the effective priority date of **June 23, 1999** of U.S. Provisional Application 60/141037. Thus, the primary reference Weimann falls and so does the Baker reference. Therefore, present claims are not obvious over Weimann in view of Baker and hence, this rejection should be withdrawn.

B. Claims 119-121 and 123 are rejected under 35 U.S.C. §103(a) as being unpatentable over Weimann (2001) in view of Tang *et al.* (WO 01/53312- dated July 2001).

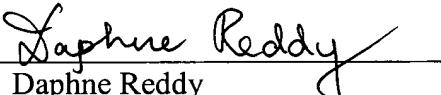
For the reasons discussed above under utility, Applicants believe that they are entitled to the effective priority date of **June 23, 1999** of U.S. Provisional Application 60/141037. Thus, the primary reference Weimann falls and so does the Tang reference. Therefore, present claims are not obvious over Weimann in view of Tang and hence, this rejection should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C26). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

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Daphne Reddy
Reg. No. 53,507

HELLER EHRLICH, LLP
Customer No. 35489
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

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